UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 CFR 1.53(b))	Attorney Docket No. 41565/196752
	First Inventor or Application Identifier: William Paul JACKSON
	Title of Invention: PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES AND DERIVATIVES THEREOF

ADDRESS TO: **ASSISTANT COMMISSIONER FOR PATENTS**
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WASHINGTON, DC 20231

Transmitted herewith for filing in the United States Patent Office is a patent application for:

Inventors: William Paul JACKSON

1. ☒ The Filing Fee has been calculated as shown below:

	No. Filed	No. Extra	Small Entity Rate	Small Entity Fee 0	Large Entity Rate	Large Entity Fee 0
BASIC FEE				$0		$0
TOTAL CLAIMS:	17 - 20 =	0	X 9 = $0		x 18 = $0	
INDEP CLAIMS:	2 - 3 =	0	X 39 = $0		x 78 = $0	
[☐]MULTIPLE DEPENDENT CLAIMS PRESENTED			+130 = $		+260 = $	
*If the difference in Column 1 is less than zero, enter "0" in Column 2.			TOTAL $ 690		TOTAL $	

The Commissioner is hereby authorized to credit overpayments or charge the following fees to Deposit Account No. 16-0605.

a. ☐ Fees required under 37 CFR 1.16 (National filing fees).
b. ☐ Fees required under 37 CFR 1.17 (National application processing fees).

☐ A check in the amount of $ ___ for the filing fee is enclosed.

☒ **The above filing fee will be paid along with Applicant(s) Response to the Notice to File Missing Parts.**

2. ☒ Specification; Total Pages 13

3. ☐ ___ Sheets of Formal Drawing(s) (35 USC 113)

4. ☒ Declaration and Power of Attorney; *[Total Pages 3]*
   a. ☐ Newly executed (original or copy)
   b. ☒ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 16 completed)
   i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) & 1.33(b).

5. ☐ Microfiche Computer Program (Appendix)

6. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s) (including a check for the $40.00 fee)

8. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*; ☐ Power of Attorney

9. ☐ English Translation Document *(if applicable)*

10. ☐ Information Disclosure Statement (IDS)/PTO-1449; ___ Copies of IDS Citations

11. ☐ Preliminary Amendment

12. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*

13. ☒ Small Entity Statement(s)
    ☒ Statement filed in prior application; status still proper and desired.

14. ☒ Priority of Great Britain Patent Application No. 9703992.9, filed 26 February 1997 was claimed under 35 USC 119 in the parent application.

15. ☐ Other: ___

16. **If a CONTINUING APPLICATION**, *check appropriate box and supply the requisite information below and in a preliminary amendment:*

☒ Continuation ☐ Divisional ☐ Continuation in Part (CIP)
of prior Application No: 09/383,078; Filed August 26, 1999

Prior Application Information: Examiner F. Powers Group/Art Unit: 1613

For CONTINUATION or DIVISONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. **CORRESPONDENCE ADDRESS**

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Attorney's Docket No. 041565/185573

Applicant: William Paul JACKSON
Application No.: Not yet assigned
Filed: [herewith]
Title: PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES

STATEMENT CLAIMING SMALL ENTITY STATUS
(37 C.F.R. § 1.9(f) & 1.27(c)) – SMALL BUSINESS CONCERN

I hereby declare that I am:

[ ] the owner of the small business concern identified below:
[×] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN: Rolabo, SL

ADDRESS OF SMALL BUSINESS CONCERN: Balmes 85-3
E-08008 Barcelona
SPAIN

I hereby state that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. 121.1301-1305, and reproduced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

[x] the specification filed herewith with title as listed above.
[ ] the application identified above.
[ ] the patent identified above.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern, or organization having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent

inventor under 37 C.F.R. 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 C.F.R. § 1.9(d), or a nonprofit organization under 37 C.F.R. § 1.9(e).

Each person, concern, or organization having any rights in the invention is listed below:

[X] no such person, concern, or organization exists.
[ ] each such person, concern, or organization is listed below.

Name: _____

Address: _____

☐ Individual ☐ Small Business ☐ Nonprofit Organization

Name: _____

Address: _____

☐ Individual ☐ Small Business ☐ Nonprofit Organization

Separate statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R. § 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b))

NAME OF PERSON SIGNING: ALEJANDRO SUREDA

TITLE OF PERSON OTHER THAN OWNER: MANAGING DIRECTOR

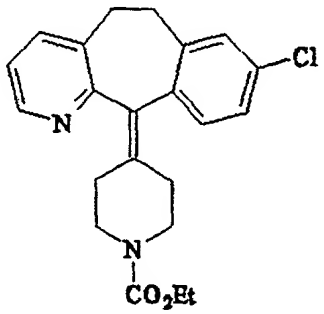
ADDRESS OF PERSON SIGNING: BALMES, 85, 3 - 08008 Barcelona

SIGNATURE: _____ DATE: Sept 27th, 1999

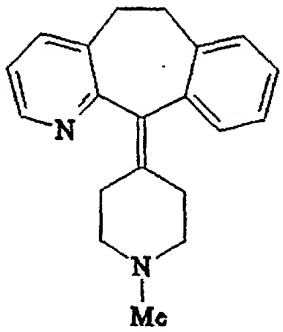
PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES AND DERIVATIVES THEREOF

The present invention relates to a process for the preparation of 10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-enes such as loratadine.

The anti-histamine ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylate (loratadine) is a potent, long acting derivative of azatadine which shows negligible CNS side effects.



LORATADINE



AZATADINE

The presence of the chlorine atom at the 8-position makes the chemistry of loratadine uniquely problematical

and reductive preparations are ineffective because of the removal of chlorine at the 8-position.

US-A-3,326,924 (Villani *et al*) discloses processes for preparing various aza-dibenzo[a,d]-cycloheptene derivatives which involve production of a tricyclic ketone which is reacted with a Grignard reagent derived from 4-chloro-N-methyl piperidine. Dehydration gives the N-methyl product. The process is, however, hindered by the amount up to 30% of 1,6-addition product which is generated in the Grignard reaction causing problems in yield and purification. US-A-4,282,233 (Villani) discloses the preparation of loratadine from the product of the above reaction by demethylation/carboethoxylation.

A synthetic route to loratadine is disclosed in US-A-4,659,716 (Villani *et al*), US-A-4,731,447 (Schumacher *et al*), US-A-4,873,335 (Schumacher *et al*) and Journal of Organic Chemistry, 1989, Vol 54,2242-2244 (Schumacher et al.) which involves alkylation of the dianion of the t-butylamide of 2-cyano-3-methyl-pyridine, re-generation of the nitrile, Grignard reaction, cyclisation with HF/BF_3 and demethylation/ carboethoxylation. This process is, however, hampered by the need to use hazardous organometallic reagents (LDA or butyl lithium) and a super-acid environment of liquid HF and BF_3 gas.

Cid *et al* have reported (Tetrahedron, 1988, Vol 44, 6197-6200) that cross coupling reactions between a tricyclic ketone and a cyclic ketone can take place using low valent titanium to give biphenylmethylene piperidines or cyproheptadine. The process suffers from the disadvantages that low valent titanium has to be generated using lithium metal which is hazardous on industrial scale and by the need to use about 12 equivalents of titanium reagent to prevent the reaction stopping at the diol stage.

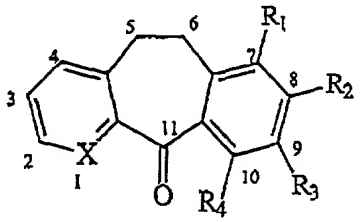
In general there exists a need for improved processes for preparing 10,11-dihydro-5H-dibenzo[a,d]-

cycloheptenes which use less hazardous materials and provide improved yields and selectivity, particularly on industrial scale production. The present invention seeks to provide such an improved process.

It has now surprisingly been found that hetero-coupling of a tricyclic aromatic ketone with an aliphatic cyclic ketone in the presence of low valent titanium gives a high yield of unsaturated coupled product with only traces of homo-coupled ketones. Typically, the low valent titanium is present as titanium (II) and only a slight excess of titanium reagent is required.

Thus viewed from one aspect the present invention provides a process for preparing 5,6-dihydro-11H-dibenzo[a,d]cyclohept-11-enes comprising reacting a dibenzosuberone or an aza derivative thereof with an aliphatic ketone in the presence of low valent titanium, ie. Ti(O), Ti(I) or Ti(II) wherein said low valent titanium is generated by zinc. Preferably the low valent titanium consists essentially of Ti(II).

Preferably the dibenzosuberone or aza derivative thereof compound is of formula I:



(I

(wherein:

X denotes nitrogen or CH;

and R^1, R^2, R^3 and R^4 which may be the same or different independently denote hydrogen or a halogen (eg. F, Cl or Br)).

Preferably the dibenzosuberone compound is one in which R^2 denotes a halogen (eg. chloro) and R^1, R^3 and R^4

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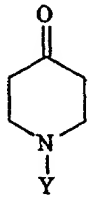
denote hydrogen and particularly preferably in which in addition X is nitrogen.

In further embodiments, X which is nitrogen may be at the 2, 3 or 4 position as defined in formula I.

Preferably the aliphatic ketone is cyclic and particularly preferably is an optionally N-substituted piperidone compound, for example a compound of formula II:



(wherein:

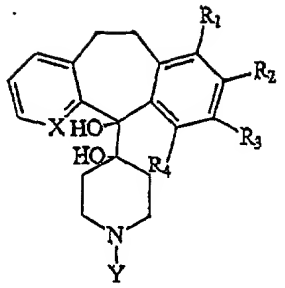
Y denotes hydrogen, lower alkyl (eg C_{1-6}-alkyl), CO_2R^5, SO_2R^5, $CON(R^5)_2$, $SO_2N(R^5)_2$, CO_2COR^5 or a N-protecting group; and

R^5 is hydrogen, a C_{1-12}-alkyl (preferably C_{1-6}-alkyl) group optionally substituted by one or more amino or C_{1-6}-alkylamino groups, a phenyl group optionally substituted by one or more halo or C_{1-6}-alkyl groups, a C_{7-12}-phenylalkyl group optionally substituted at the phenyl by one or more halo or C_{1-6}-alkyl groups, 2-piperidyl, 3-piperidyl or piperidyl substituted at the nitrogen atom by a C_{1-4}-alkyl group);
and the salts thereof.

Preferably the piperidone is one in which Y is the group CO_2Et.

The reaction proceeds via an intermediate diol which, if desired, may be isolated by conducting the reaction at a lower temperature. The olefin may be prepared from the intermediate diol in a subsequent step in a conventional manner.

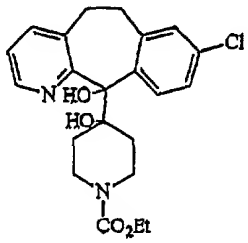
The diol intermediate itself is novel and forms a further aspect of the invention. Thus the present invention provides a compound of formula III:



(III

(wherein R_1, R_2, R_3, R_4, X and Y are as defined hereinbefore).

The preferred compound is:



The dibenzosuberone and aliphatic ketone reagents are preferably reacted in substantially equimolar quantities; however an excess of either reagent can be tolerated, eg. the two reagents may be present in molar ratios of from 1:2 to 2:1, preferably 1.5:1 to 1:1.5, especially preferably 1.1:1 to 1:1.1.

Low valent titanium may be prepared *in situ*, using zinc eg. by reaction of a Ti(III) or Ti(IV) compound or complexes thereof with zinc. In one preferred embodiment of the method according to the invention, a combination of titanium (IV) chloride or a complex thereof and zinc is used to generate low valent titanium. This embodiment has the advantage that zinc is relatively cheap and safe to use on an industrial scale. A combination of titanium (III) chloride and zinc may be used with equal success.

In accordance with the invention, Zn and Ti may be conveniently used in molar ratios of 4:1 to 1:1, preferably 3:1 to 2:1.

Typically, a slight molar excess of titanium reagent is used over the amount of ketone present, although a larger excess may be used if desired.

The titanium reagent is preferably used at a molar ratio of from 0.5:1 to 6:1, preferably 1.5:1 to 4:1, particularly 2:1 to 3:1 relative to the dibenzosuberone.

The reaction may be conveniently conducted in etherial solvents such as for example tetrahydrofuran, dioxane and dimethoxyethane which are commonly used in coupling reactions involving titanium. Nevertheless ethyl acetate, iso-propyl acetate, t-butylacetate, DMF and acetonitrile are equally effective for this purpose. Tetrahydrofuran is preferred.

The reaction temperature may be conveniently in the range -10°C to the reflux temperature of the chosen solvent, but is preferably 100°C or less, especially 20 to 60°C. To prepare the diol the reaction temperature is preferably below 10°C.

As noted above, Y may represent an N-protecting group and suitable groups includes acetyl, benzoyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxy benzyl or 2,4-methoxybenzyl groups. The optional subsequent cleavage of a N-protecting group may for example be carried out by conventional means eg. hydrolytically, hydrogenolytically or in the presence of an oxidising agent or acid. Further examples of N-protecting groups and appropriate deprotection reactions are described in the literature (see for example McOmie, "Protecting groups in organic chemistry", Plenum, 1973 and Greene, "Protective groups in organic synthesis", Wiley Interscience 1981).

The process according to the invention is typically carried out at elevated temperature (eg. under reflux)

for at least one hour, preferably 1-4 hours, particularly preferably 1-2 hours and at ambient pressure.

The process according to the invention provides a yield of a 10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene typically in excess of 60% and often 80% or more.

The invention is illustrated in a non-limiting fashion by the following examples in which all ratios and percentages are by weight unless otherwise stated:

EXAMPLE 1

Preparation of ethyl 4-(5,6-dihydro-11H-benzo[5,6]cycloheptan)-piperylidene-1-carboxylate

A mixture of 4-carboethoxypiperidone (5.64g, 33 mmole) and dibenzosuberone (6.24g, 30 mmole) are dissolved in tetrahydrofuran (82 ml) under a nitrogen atmosphere. Zinc (8.83g, 135 mmole) is added and the mixture cooled to 0°C. Titanium tetrachloride (7.4 ml, 67.5 mmole) is added over 15 minutes so that the temperature does not exceed 30°C. The mixture is then heated at reflux for about 1.5 hours.

About 50 ml of THF is removed by distillation under reduced pressure and the residue is partitioned between toluene (100 ml) and 2M HCl (100 ml). The layers are separated and the aqueous phase extracted with a further 100 ml toluene. The combined organic phase is washed with 50 ml 10% potassium carbonate solution and dried over magnesium sulphate.

Removal of the solvent and chromatography of the residue (10.3g) on silica gel using ether:dichloromethane (5:95) gives 9.3g (89%) product at constant weight as a viscous oil which crystallises on standing to give a solid (MP 87-90°C).

EXAMPLE 2

Preparation of ethyl 4-(5,6-dihydro-11H-benzo[5,6]cycloheptan)-piperylidene-1-carboxylate

A mixture of 4-carboethoxypiperidone (3.8g, 22 mmole) and dibenzosuberone (4.4g, 20 mmole) are dissolved in ethyl acetate (50 ml). Zinc (6.4g, 100 mmole) is added and the mixture cooled to 0°C. Titanium tetrachloride (4.9 ml, 45 mmole) is added over about 5 minutes so that the temperature stays below 15°C. (If required, the diol may be isolated at this stage by addition to water.) The reaction is heated to reflux for 2 hours. The mixture is allowed to cool and 75 ml 2M HCl is added. The aqueous phase is extracted with a further 50 ml ethyl acetate. The combined organic phase is washed with 50 ml 10% potassium carbonate solution and dried over magnesium sulphate.

The solvent is removed to constant weight under vacuum to give 6.8g crude product which is contaminated with a small amount of deoxygenated tricycle.

EXAMPLE 3

Preparation of Loratadine

8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (2.45g, 10 mmole) (see J. Heterocyclic Compounds, vol. 8, 1971, page 73) and 4-carboethoxypiperidone (1.8g, 10 mmole) are dissolved in 30 ml tetrahydrofuran. Zinc (5g, 78 mmole) is added and the mixture cooled to 0°C. Titanium tetrachloride (3 ml, 27 mmole) is added over about 10 minutes. The mixture is then heated at reflux for 1 hour. The mixture is added to 100 ml water and 50 ml toluene. Most of the aqueous phase is separated and the organic phase is washed with 20 ml ammonium hydroxide solution.

The mixture is filtered through celite and the celite washed with a further 50 ml toluene. The organic

phase is separated and dried over magnesium sulphate.

The solvent is removed and the residue (3.75 g) is crystallised from butyl ether to give 2.5g loratadine (68%). HPLC shows the product to be >98% pure.

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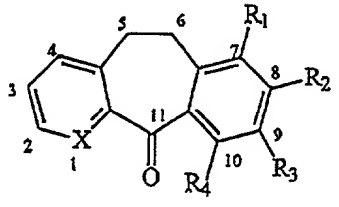
CLAIMS

1. A process for preparing 5,6-dihydro-11H-dibenzo[a,d]cyclohept-11-enes comprising reacting a dibenzosuberone or an aza derivative thereof with an aliphatic ketone in the presence of low valent titanium wherein said low valent titanium is generated by zinc.

2. A process as claimed in claim 1 wherein said dibenzosuberone or aza derivative thereof is of formula I:



(I

(wherein:

X denotes nitrogen or CH;

and R^1, R^2, R^3 and R^4 which may be the same or different independently denote hydrogen or a halogen).

3. A process as claimed in claim 2 wherein R^2 is a halogen.

4. A process as claimed in claim 2 or 3 wherein R^1, R^3 and R^4 denote hydrogen.

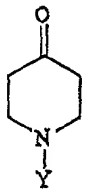
5. A process as claimed in any of claims 2, 3 or 4 wherein X is nitrogen.

6. A process as claimed in any preceding claim in which the aliphatic ketone is cyclic.

AMENDED SHEET

7. A process as claimed in claim 6 wherein said cyclic aliphatic ketone is an optionally N-substituted piperidone.

8. A process as claimed in claim 7 wherein said piperidone is of formula II:



(wherein:

Y denotes hydrogen, lower alkyl, CO_2R^5, SO_2R^5, $CON(R^5)_2$, $SO_2N(R^5)_2$, CO_2COR^5 or a N-protecting group; and

R^5 is hydrogen, a C_{1-12}-alkyl group optionally substituted by one or more amino or C_{1-6}-alkylamino groups, a phenyl group optionally substituted by one or more halo or C_{1-6}-alkyl groups, a C_{7-12}-phenylalkyl group optionally substituted at the phenyl by one or more halo or C_{1-6}-alkyl groups, 2-piperidyl, 3-piperidyl or piperidyl substituted at the nitrogen atom by a C_{1-4}-alkyl group)

and the salts thereof.

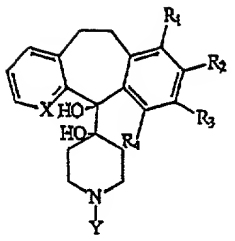
9. A process as claimed in claim 8 wherein Y is CO_2Et.

10. A process as claimed in any preceding claim wherein Ti is present in a molar ratio range 1.5:1 to 4:1 relative to the dibenzosuberone.

11. A process as claimed in claim 10 wherein Ti is present in a molar ratio range 2:1 to 3:1 relative to the dibenzosuberone.

12. A process as claimed in any preceding claim comprising the preparation of an intermediate diol of

formula III:



(III

(wherein R_1, R_2, R_3, R_4 and X are as defined in claim 2 and Y is as defined in claim 8).

13. A process as claimed in any preceding claim wherein said low valent titanium consists essentially of Ti(II).

14. A process as claimed in any preceding claim wherein low valent titanium is prepared *in situ*.

15. A process as claimed in claim 14 wherein low valent titanium is prepared by reacting a Ti(III) or Ti(IV) compound or complex with said zinc.

16. A process as claimed in claim 15 wherein said titanium compound is titanium(III) chloride or titanium(IV) chloride or a complex thereof.

17. A process as claimed in any preceding claim for preparing Loratadine.

ABSTRACT

A process for preparing 10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-enes (e.g. loratadine) by reacting a dibenzozuberone with an aliphatic ketone in the presence of low valent titanium.

Attorney Docket No. 041565/185573

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
(Foreign Agent Involved)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES

the specification of which is attached hereto and was filed on February 26, 1998 as PCT International Application Number PCT/GB98/00605 designating the United States.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) Claimed			**Priority**
PCT/GB98/00605	PCT	February 26, 1998	☒ Yes ☐ No
(Number)	(Country)	(Day/Month/Year Filed)	
9703992.9	Great Britain	February 26, 1997	☒ Yes ☐ No
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefits under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C., § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Appln. Serial No.)	(Filing Date)	(Status --patented/pending/aban.)
PCT/GB98/00605	February 26, 1998	pending

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from my British representatives, Frank B. Dehn & Co., as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

I hereby appoint the practitioners associated with the firm of ALSTON & BIRD, LLP to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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